Establishing the limits of normal cerebral ageing and senile dementias

KAREN RITCHIE

Cognitive deterioration is so commonly observed in the elderly that it is considered by many to be an inevitable feature of the ageing process. Some researchers have proposed that the senile dementias are the inevitable end-point of this process, should the person live long enough. The differentiation of normal cerebral ageing from disease process is important in the selection of control groups for research, and also for clinical decision-making. In the latter context it is important to ask at what level of dysfunction intervention should occur, and whether this should be active or palliative. Cognitive change in the elderly is here considered from biological, neuropsychological and epidemiological viewpoints. Current research suggests that senile dementia is the result of the interplay of genetically determined disease processes, ageing-related decline which may be regulated at a cellular level, and neuronal repair and compensation mechanisms. Therefore, to debate whether dementia is simply an extension of a normal ageing process or not is probably too simplistic an approach.

DEFINING AGE-APPROPRIATE FUNCTIONING

> "You are old father William"
> The young man said
> "And your hair has become very white
> And yet you incessantly stand on your head
> Do you think at your age it is right?"
>
> (Lewis Carroll, *Alice in Wonderland*, 1865).

The problem of defining age-appropriate physical and mental functioning, quaintly evoked by Lewis Carroll at the end of the 19th century, is perhaps one of the most challenging questions facing psychogeriatric research in this decade. While considerable effort has been expended in an attempt to internationally standardise diagnostic criteria for psychiatric disorder, the concept of 'normality', has been relatively overlooked. Psychogeriatric disorders in general, being diagnosed principally on the basis of non-specific behavioural criteria, implicitly refer to a normal range. However, an examination of clinical and epidemiological studies reveals wide discrepancies with regard to the selection of control populations reflecting quite different underlying theoretical assumptions. At a general level it is surprising that normative values for 'the elderly' are often based on mean performance data derived from populations with an age range from 60–100 years; no competent researcher would refer to 'the young', combining data from age 10–50 years. This is principally because of our advanced state of knowledge with regard to infantile and young adult cognitive functioning as compared with cerebral ageing. The choice of normative groups for the elderly is an important question as it is undoubtedly a major component of inter-study variability.

Conceptual assumptions concerning the normal limits of cerebral ageing, and the inevitability of progressive cognitive decline, determine not only research design but also clinical practice. Within a research context it raises the question of whether aetiological models for the dementias should be sought which are different from those associated with normal biological ageing. In clinical practice it underlies the decision as to whether palliative care only should be provided in keeping with the assumption of an inevitable natural devolution, or whether active therapeutic intervention should be initiated based on the assumption that decline at any age should be considered pathological. The present discussion is aimed at describing changing conceptualisations of the ageing process in general, and the place of the dementias in relation to normal cerebral ageing.

CURRENT CONCEPTUALISATIONS OF 'NORMAL' CEREBRAL AGEING

There are few who would dispute that some loss of physical and mental function is inevitable over time due to accumulated biological stress, injury and atrophy. There is some evidence to suggest that senescence may be programmed at a cellular level (Wyllie *et al*, 1980), with recent research in this area describing the role of telomeres, or 'mitotic clocks', which trigger the senescent process after a limited number of cell reproductions (Bodnar *et al*, 1998). The central question here, however, is to determine the extent to which our observations of change in elderly populations may be attributable to an inevitable biological ageing process and to what extent they may be attributed to disease. At a conceptual level Ritchie *et al* (1994) have drawn a distinction between 'ageing-related' and 'age-related' disorders in order to distinguish diseases which are a result of the ageing process itself, and which may be considered universal should the person live long enough, from diseases which have a high prevalence among elderly persons. The pathogenesis of ageing-related disease is directly related to the ageing of the individual with morbidity increasing exponentially with chronological age, while age-related diseases (such as Huntington's chorea) occur at a given age interval and then decline in frequency or continue at less than an exponential rate of increase. From an epidemiological point of view 'age-related' disorders may be expected to have a higher incidence in a vulnerable subgroup of the population for all or part of the senescent period but do not necessarily increase proportionally to known biological ageing processes, as is the case in ageing-related disease.

The application of this simple dichotomous model to observed behavioural change in the elderly is extremely difficult in the face of our uncertainty as to what is biologically normal. Reviewing the debate over 'normal' values of blood pressure and blood sugar levels, and whether the values justifying treatment should be age-adjusted, Manton & Stallard (1988) conclude that:

> "... such an age criterion is tending to disappear, suggesting that the 'normal' state for the elderly is not necessarily very different than for younger persons".

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They make the point that even changes in biological functions once considered to constitute in themselves markers of the ageing process, are progressively being reassigned to the category of treatable pathology rather than normal ageing. An example of this is resting cardiac output, which is now considered not to decline significantly between the ages of 30 and 80 years when latent cardiac disease is screened out.

Manton & Stallard's observations are further supported by longitudinal studies of health status in the elderly which suggest overall that the health of the elderly is improving due to a situation of 'dynamic equilibrium' in which, although the prevalence of chronic diseases increases with the fall in mortality, the diseases themselves are less severe due to symptomatic treatment and early prevention programmes, and thus generate lower levels of dependency (Manton *et al*, 1988; Jagger *et al*, 1991; Robine *et al*, 1997). These findings together suggest that what is considered to be the normal state of health for elderly people is being fixed at increasingly higher thresholds. If such changing conceptualisations are not carried over into clinical practice, elderly persons are likely to be under-treated.

A similar conceptual shift has taken place, at least at a theoretical level, with regard to cerebral ageing and mental health. While it is generally accepted that a certain number of ageing-related changes in the central nervous system are probably universal and independent of disease processes (neuronal shrinking, enlargement of ventricles, loss of dendritic branches and synaptic connections), neuronal reserves, in the absence of disease or trauma, are generally considered sufficient to ensure a far higher level of cognitive performance than has been supposed on the basis of cross-cultural, age-cohort comparisons. A part of the problem has been negligence of cohort or generation effects which has led to a serious under-rating of the capacities of the elderly. This is demonstrated by the longitudinal studies of Schaie and Willis (Schaie, 1983; Schaie & Willis, 1991) who observed that whereas cross-sectional comparison of adults at different ages showed significant decline with age, 20-year follow-up of the same individuals demonstrated relative stability across time, until the individuals reach their early 80s where it might be expected that sensory deficit and physical illness explain a significant proportion of the decline. This study not only suggests that age-group comparisons may overestimate age-related cognitive decline, but also points to evolution in cognitive function. That is, elderly people today perform significantly better than elderly people from the previous generation, due to factors such as improved health care, nutrition and education.

Laboratory studies of cognitive functioning have consistently demonstrated that while decrements in medium-term or secondary memory with age are directly related to increased ageing-related loss of neurones in the hippocampus, amygdyla and locus coeruleus (Craik, 1977; Crook *et al*, 1979; Ferris *et al*, 1980), working (immediate) memory, semantic memory and other linguistic abilities remain stable in the absence of dementia (Craik, 1977; Baddeley *et al*, 1986; Huff *et al*, 1986). A longitudinal general population study of elderly people conducted in the South of France, using a computerised battery of cognitive tests supplemented by neurological examination and cerebral imagery (Ritchie *et al*, 1996; Leibovici *et al*, 1996) has demonstrated that low levels of cognitive impairment in the 'normal' elderly constitute homogeneous subtypes, and are largely attributable to physical illness, depressive symptomatology and prodromal signs of senile dementia. When such groups are removed from the 'normal' group, the remaining subjects show improvement rather than deterioration over a three-year period, with education rather than age explaining much of the variance. That is, a significant proportion of the decline seen in elderly people may be attributed to pathology rather than an ageing process. The results of this study also demonstrate the great heterogeneity seen in patterns of cognitive ageing, the confounding effects of undiagnosed neuropathology in statistical analyses, and the increased vulnerability of persons with low IQ after the age of 75 years. Finally, the study suggests that the age of 70 may be a more appropriate cut-off point for the 'aged', in the context of cognitive functioning, rather than age 60.

NORMAL CEREBRAL AGEING AND SENILE DEMENTIAS

Generally speaking, two conceptual frameworks have evolved to explain the relationship of the senile dementias to normal ageing-related changes. The first, derived from cognitive psychology and the normative model, makes no distinction between sick and well populations but rather proposes a continuum along a normal distribution from high performance levels, through mild cognitive impairments such as age-associated memory impairment (Crook *et al*, 1986) to the senile dementias. Alternatively, the dichotomous medical model, which makes a clear distinction between well and ill populations, implies discontinuity between normal cerebral ageing and the senile dementias. Overlap may occur between sick and well populations only where diagnosis is uncertain or symptomatology has not yet reached clinical levels.

Adherents of the continuum hypothesis determine the limits for senile dementia by fixing a cut-off point along a continuous range of cognitive decline which is determined predominantly by social and individual tolerance of symptoms. Dementia is thus construed as the end-point in the normal process of cerebral ageing, which we shall all develop if we live long enough. Adherents of the medical model on the other hand maintain that dementia involves a pathological process related to aetiological factors different from those involved in normal ageing, although there may be interaction with ageing-related processes. Evidence for whether dementia should be construed within a continuum or medical model, that is as a disease or part of natural ageing, will here be considered from the point of view of current research in biology, cognitive psychology and epidemiology.

Biological evidence

At a biological level, senile plaques and neurofibrillary tangles, which are considered to be the principal criteria for the confirmed diagnosis of the principal form of senile dementia, Alzheimer's disease, are also found in normal ageing, thus suggesting a continuum. Internationally accepted neuropathological criteria for Alzheimer's disease provide age-adjusted threshold levels for plaques and tangles in specific parts of the brain based on density alone (Khachaturian, 1985). Additionally, credible biological models of common pathways to both normal ageing and senile dementia have been proposed; for example theories of programmed neuronal apoptosis (Cotman & Anderson, 1995), free radical neurotoxicity (Bondy, 1992) and defective DNA repair (Itzhaki, 1994). The lack of a

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specific biological marker for the senile dementias has remained one of the most convincing arguments in favour of a conceptual continuity between normal ageing and dementia.

More recently, some evidence has been advanced for qualitative differences at a biological level. Differences have been noted, for example, in the regional localisation and staging of Alzheimer's disease-related changes. In normal elderly people senile plaques are found almost exclusively in the superficial cortex, whereas in people with Alzheimer's disease they descend to the whole depth of the cortex (Esiri, 1997). Gomez-Isla *et al* (1996) also note distinctive profound loss of layer II entorhinal cortex neurons in very early Alzheimer's disease which is not typical of normal ageing. West *et al* (1994) have demonstrated different patterns of neuronal loss in the hippocampus in Alzheimer's disease and normal ageing; consistent and significant loss being reported in the pyramidal cell layer of CA1 in Alzheimer's disease only. In an excellent review of the causes of neuronal death in ageing, Morrison & Hof (1997) point to the importance of stereological techniques in this area which demonstrate that neuron death is restricted in normal ageing and does not account for dementia-related impairment of neocortical and hippocampal functions. This conclusion is further supported by the longitudinal cerebral imaging studies of normal ageing and senile dementia conducted in Oxford by Jobst *et al* (1994) which show that in the case of Alzheimer's disease there is a sudden onset of rapid, catastrophic atrophy occurring in specific areas of the medial temporal lobe inconsistent with the notion of a progressive ageing process.

Politoff & Monson (1996) have demonstrated through electroencephalogram studies that normal ageing is associated with posterior increases in the alpha band and decreases in the delta band in anterior regions in comparison with younger adults. According to the continuum hypothesis, subjects with Alzheimer's disease should demonstrate alpha and delta values which are extensions of these upward and downward trends. While significantly different from the normal subjects, the subjects with Alzheimer's disease were found on the other hand to show a trend in the opposite direction, suggesting that normal ageing and Alzheimer's disease affect different neuronal populations. This finding has recently been replicated by Jonkman (1998).

The general question has also been raised as to whether the neurological changes observed in Alzheimer's disease might not, at least in part, represent a reaction to a pathological process, rather than constituting the pathology itself. With regard to neurofibrillary tangles, for example, it has been established that amyloidosis, which heralds the onset of Alzheimer's disease, is followed by the appearance of tangles as a secondary response to neuronal degeneration (Delacourte *et al*, 1988); tangles being a non-specific response to a wide range of aggressions to the neurone population (Delacourte & Buée, 1997). In normal ageing the reverse is observed with the appearance of tangles only in the absence of amyloid (Jellinger, 1995) as a response principally to ageing-related cell loss in the hippocampus. In conclusion, biological evidence suggests that changes in the central nervous system observed at higher ages are due to the interaction of three separate processes; disease, ageing-related decline and neuronal repair mechanisms.

Evidence from cognitive psychology

At a clinical level early senile dementia cannot readily be distinguished from benign impairment and diagnosis is usually made by reference to deviations on cognitive tests from age-adjusted normative data. Longitudinal studies of cognitive performance in elderly cohorts have also suggested many similar changes in normal ageing and senile dementia, with dementia being diagnosed beyond a critical threshold (Flicker *et al*, 1993; Albert, 1994). Scores from studies of normal subjects and subjects with dementia are commonly seen in a graphic representation to form a continuous slope from the highest to the lowest level. Brayne & Calloway (1988) interpret this continuous distribution of scores as proof that normal ageing and dementia lie on a continuum. The lack of a clear break between scores obtained by persons with and without dementia may, however, largely be explained by subclinical pathology occurring in early stages of dementia leading to misclassification of dementia subjects as normal, and thus giving an impression of continuity in a situation of discontinuity. The problem is well illustrated by the longitudinal study conducted by Storandt *et al* (1994) in which nine out of 20 control subjects used in a case–control study were found at autopsy to meet neuropathological criteria for Alzheimer's disease. Reallocation of these subjects to the clinical group greatly increased the divergence in scores.

Laboratory studies of cognitive functioning in senile dementia and normal ageing suggest many similarities between normal ageing and dementia; subjects with dementia manifesting greater levels of dysfunction. However, impairments which appear to be specific to dementia have also been identified, notably in the visuospatial and attentional allocation components of short-term memory (Baddeley, 1986; Morris, 1986; Sahakian *et al*, 1988) and in semantic memory (Appell *et al*, 1982; Martin & Fedio, 1983). Overall, the changes observed in information processing studies are suggestive of a pathological process which both accelerates the process of normal cognitive ageing and provokes significant decline in cortical areas normally relatively spared. Moreover, patterns of cortical dysfunction paralleling the cognitive changes seen in senile dementia are not uniform, with unilateral or predominantly frontal localisations being observed (Mayeux *et al*, 1985; Martin *et al*, 1986; Ritchie & Touchon, 1992). Similar patterns of deficit cannot be found in cluster analytic studies conducted on normal ageing populations (Valdois *et al*, 1990; Leibovici & Ritchie, 1995).

Epidemiological evidence

If senile dementia is simply cerebral old age, then it is to be expected that at a population level the prevalence and incidence of the dementias should increase with age, converging towards 100% at the extremes of life expectancy. Epidemiological studies of senile dementia have indeed consistently demonstrated that age is a highly significant risk factor for dementia with prevalence rates rising exponentially from the age of 60 years onwards (Jorm *et al*, 1987; Ritchie *et al*, 1992). These observations are strongly suggestive of an ageing-related disorder.

More recently a meta-analysis of prevalence studies of senile dementia conducted on population studies which have examined rates at very high ages (85–100 years) has demonstrated a logistic relationship with age (Ritchie & Kildea, 1995); that is, the increase in dementia prevalence appears to slow down over the age of 80,

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flattening out to zero increase at the age of 95, with a prevalence rate of 40%. This result is highly suggestive of an age-related rather than an ageing-related disorder, in which a disease process with penetrance at higher ages is triggered off by, but is not part of, the ageing process. This analysis is, however, based on prevalence data which do not take into account changes in survival rates (that is, the number of cases may continue to increase but the duration of survival becomes shorter). However, the finding has received some verification from longitudinal studies of dementia incidence at very high ages (Ebly *et al*, 1994; Fichter *et al*, 1995; Johansson & Zarit, 1997). McGee & Brayne (1998) have attempted to evaluate the validity of the logistic model by estimating incidence from prevalence, concluding that when mortality rates are taken into account that the incidence of dementia is very high (30% of elderly people at age 100 years). The study is inconclusive, due to a number of theoretical and mathematical shortcomings related to the choice and application of only one possible mortality odds ratio and the unavailability of mortality rates above the age of 85 (these have been extrapolated from an exponential model and lead to unacceptably wide confidence intervals).

Calculations of dementia-free life expectancy (derived from the adjustment of observed population mortality rates by disease prevalence rates) show a reduction in dementia-free life expectancy with age (Ritchie, 1994; Ritchie *et al*, 1994). The percentage of life spent without dementia for women falls by around 10% in the decade between the late 70s and late 80s in France and Australia, and up to 20% in the UK. However, even at very great ages the proportion of remaining life expected to be lived without dementia remains very high. Using a regression model to project towards the upper limits of life expectancy it was found for France, that at age 97 years life expectancy without dementia still occupies 67% of remaining life expectancy, and that the average human life expectancy would in fact have to go beyond 170 years of age under present survival conditions before dementia took up all life expectancy. This suggests that it is highly unlikely that all persons will have dementia even if everyone lives to a very great age.

It would appear that ageing is not as catastrophic a process as we have often tended to assume. As causes of disability are identified and treated it is possible that an increasing number of conditions will be reclassified from 'just old age' to 'treatable pathology'. Is senile dementia itself an ageing-related disorder? It is impossible to conclude at present. Current evidence suggests a neuropathological process aggravated (if not triggered) by ageing-related changes, injury and cardiovascular pathology in genetically vulnerable individuals. Not all individuals appear to develop dementia even if they live for an exceptionally long time. The same situation has already been observed in relation to some cancers. Such a disease does not easily fit the 'age-related'–'ageing-related' model. Kohn (1982) has proposed what is probably a more satisfactory three-dimensional model of the relationship of disease to age, distinguishing diseases whose incidence increase with age, diseases which are ageing processes and diseases which interact with the ageing process. A distinction may thus be made between age-related, ageing-related and 'age-related'–'ageing-accelerated' disorders. The latter category refers to diseases whose onset and course may be determined by an interaction of genetic and ageing-related changes. This conceptualisation probably best describes our present knowledge of the dementias and their relationship to the process of normal cerebral ageing.

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